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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

Re: Docket No. 2005P-0411
Comments to Citizen Petition Filed on Behalf of Wyeth

Dear Sir or Madam:

The International Academy of Compounding Pharmacists (IACP) respectfully submits these comments pursuant to 21 C.F.R. § 10.30(d) to the October 6, 2005 Citizen Petition filed by Wyeth, to correct the erroneous and misleading statements in Wyeth's Citizen Petition. IACP is an international non-profit association devoted to the protection and advancement of pharmaceutical compounding -- one of the essential elements of the profession of pharmacy and the U.S. healthcare system. IACP's membership consists of more than 1,500 pharmacists who engage in compounding as well as approximately 200 other members, including physicians, patients, pharmacy students, and retired pharmacists. IACP's membership includes pharmacists that compound customized prescriptions upon receipt of a physician's prescription or order for bio-identical hormone replacement therapies (BHRT).

The Citizen Petition initially requests FDA to "[i]nitiate enforcement actions, in the form of seizures, injunctions and/or warning letters..." (Citizen Petition at 3). This request, aside from resting on a thoroughly flawed basis, is also improper. Citizen

Petitions may not be used to request enforcement actions, such as referrals to the U.S. Attorney for enforcement actions in court, including referrals for seizures or injunctions. See 21 C.F.R. § 10.30(k). FDA should therefore deny the Citizen Petition as seeking actions that may not be requested in a Citizen Petition.

IACP's response will focus on the major errors, inaccuracies, and mischaracterizations in Wyeth's Citizen Petition. We will not address all of the numerous factual and legal errors. It is sufficient to note that the errors we discuss are characteristic of the entire Citizen Petition. In particular, in its zeal to attack compounding, Wyeth repeatedly invokes statutory provisions that FDA has never itself said applies to compounding pharmacies.

Before we address the errors in Wyeth's petition, we would first like to reiterate that pharmacy compounding is a critical and valuable healthcare practice. Millions of Americans have unique health needs that off-the-shelf, prescription medicines cannot meet. These patients rely on customized medicines – prescribed or ordered by licensed physicians and mixed safely by trained, licensed compounding pharmacists – to treat their unique conditions. The Food and Drug Administration, the U.S. Supreme Court, Congress, and virtually every major association of healthcare professionals recognize the value of pharmacy compounding. Patients with unique needs rely more heavily on compounded medications than the general population – including home healthcare patients, hospice care patients, cancer patients, hospital patients on intravenous medicines, pain management patients, dental patients, dermatological patients, and others. Applying, as Wyeth suggests, regulations that are designed for off-the-shelf, one-size-fits-all pharmaceuticals to the practice of compounding individualized medications would, as the government acknowledges, effectively deny these patients access to these medications.

I. Wyeth Mischaracterizes Pharmacy Compounding by Deliberately Ignoring the Crucial Role of the Patient's Physician

The Citizen Petition portrays compounding pharmacies as if they were selling BHRT preparations directly to hapless patients. Indeed, Wyeth states that BHRT pharmacies "are simply trying to dupe an unsuspecting patient population." Citizen Petition, 28. However, the 36-page Citizen Petition never once acknowledges that compounding pharmacies operate within the physician/patient/pharmacy triad, and that no prescription is compounded and provided to patients without receipt of a prescription from the patient's physician.

Patients are unable to obtain compounded BHRT preparations without the involvement of their physicians. Patients cannot order BHRT – physicians must prescribe this treatment for their patients. Indeed, the marketing materials appended to the Citizen Petition expressly describe the involvement of the patient's physician -- a fact nowhere acknowledged by Wyeth.¹

Compounding pharmacies are therefore not misleading or "duping" unsophisticated patients. Indeed, a pharmacist's role in filling a prescription for BHRT is analogous to their role in dispensing Wyeth's Premarin in that both are done in response

¹ See, e.g. Metcalf Pharmacy, ("Metcalf Pharmacy works together with patients and prescribers...") (emphasis added) (Citizen Petition, Tab A); Handouts provided by Mary M. Morton, FNP-L (Citizen Petition, Tab C) ("Compounding pharmacists work together with patients and prescribers...," includes diagram of the patient/physician/practitioner triad (emphasis added); Health Max Pharmacy ("Natural hormone formulations ... are normally available in the US ... with a physician's prescription.") (Citizen Petition, Tab D); Scarbrough Medical Arts Pharmacy ("We feel it is very important for patients to understand these [BHRT] options ... and to discuss this in great detail with their doctor ... we recognize that as this patient's physician, the final decision to implement therapy is with you and ultimately, the patient.") (Citizen Petition, Tab E); Red River Pharmacy Services; ("A compounding pharmacist, pursuant to a doctor's prescription can prepare customized bio-identical hormone replacement therapy for women...") (Citizen Petition, Tab J).

to a physician's order. The marketing materials cited by Wyeth make clear the existence and importance of the triad relationship among patients, their physicians (in whom the ultimate medical decision regarding initiating appropriate HRT resides), and the compounding pharmacist. The marketing materials are clearly intended to educate patients and health care providers, and spark an important conversation between patients and their doctors.

II. Wyeth Erroneously Asserts that Compounding Pharmacies are Manufacturers

Throughout the Citizen Petition, Wyeth erroneously and baselessly characterizes pharmacies that compound BHRT formulations upon receipt of a physician's prescription as manufacturers. Wyeth's characterization is incorrect.

Wyeth asserts that compounding pharmacies "manufacture and market these [BHRT] products not as drugs compounded to address particularized patient needs in limited circumstances, but as safer and more effective wholesale substitutes for FDA-approved drug products for any woman wanting hormone therapy."² Contrary to Wyeth's characterization of compounding pharmacies as manufacturers that churn out uniform products, compounding pharmacies that compound BHRT preparations produce medicines that are customized to individual needs. Again, although Wyeth omits any reference to customization, the advertisements and promotional materials it cites make clear that BHRT preparations are compounded based on the needs of the individual, not mass-produced like Wyeth's products.³ Each Wyeth drug is offered in a single

² Citizen Petition at 2.

³ See e.g. Metcalf Pharmacy ("Metcalf ... provide(s) customized bio-identical hormone replacement therapy that meets each individual's specific needs...") (emphasis added); Handouts provided by Mary M. Morton, FNP-L ("Every woman is unique. Therefore, it is a sensible approach for the patient to work together with health care professionals to customize hormone replacement therapy. Bio-identical HRT can be compounded in the needed strength and dosage form

formulation. In sharp contrast, compounding pharmacies compound customized therapies based on the evaluation of the woman's physician as to what formula would be best for her.

A. Compounding Pharmacies are not Manufacturing Copies of Commercially Available Preparations

Wyeth asserts -- again without basis -- that all compounding pharmacies are manufacturers because they compound large quantities of copies of commercially available preparations -- assumedly, Wyeth's own HRT preparations. Specifically, the Citizen Petition claims that "BHRT pharmacies are compounding copies of FDA-approved hormone products."⁴ This is demonstrably false.

For more than a decade, Wyeth has successfully fended off generic competition to its conjugated estrogen products by asserting that the active ingredients in the conjugated estrogen products could not be adequately identified.⁵ Specifically, Wyeth has asserted, and FDA has accepted, that in addition to sodium estrone sulfate and sodium equilin sulfate, long believed to be the sole active ingredients in Premarin, estrogen delta (8, 9) dehydroestrone sulfite (DHES) originally believed to be an impurity inherent in a product derived from pregnant mare's urine, may actually be a "concomitant component" that had

and administered via the most appropriate route to meet each woman's needs."); Health Max Pharmacy ("Health Max Pharmacy is committed to providing ... specific and specialized formulations to meet patients' needs.");

⁴ Citizen Petition at 21.

⁵ See, e.g. Docket No. 94P-0429 (Wyeth Citizen Petition to Establish the Proper Composition of Conjugated Estrogens); Memorandum from Director of CDER to the Director of the Office of Generic Drugs re: Approvability of a Synthetic Generic Version of Premarin (May 5, 1997) (Woodcock Memorandum); Docket No. 98P-0311 (Wyeth Citizen Petition re: New Drug Application for Mixtures of Estrogens (May 12, 1998).

an effect on potency.⁶ Wyeth has been able to maintain its monopoly by convincing FDA that there can be no generic copy of Premarin -- and presumably its other pregnant mare urine-based drugs in its stable -- because the precise characteristics of the drug cannot be characterized. As such, BHRT preparations are not copies of commercially available drugs, because according to Wyeth's own arguments, acquiesced to by FDA, there can be no copies of Wyeth's pregnant mare urine-based drugs. Given that Wyeth has repeatedly maintained to FDA that no drugs can be the same as its HRTs, and that the BHRTs compounded by pharmacists are tailored to individual patients, compounded BHRTs are not the same as Wyeth's HRTs.

B. Advertising Does Not Make a Pharmacy into a Manufacturer

Wyeth asserts that educational promotional materials distributed by compounding pharmacies transform those pharmacies into manufacturers. Wyeth and its counsel ignore compounding pharmacies' First Amendment rights to engage in commercial speech, which is somewhat surprising given that Wyeth's legal counsel (which submitted the Citizen Petition) was responsible for submitting the briefs and arguing one of the seminal cases asserting that the First Amendment free speech protections limited FDA's ability to regulate communications about prescription drugs. See e.g. Washington Legal Foundation v. Henney, 202 F.3d 331 (D.C. Cir. 2000).

Wyeth also ignores the fact that the Supreme Court has already addressed whether advertising may be considered as a factor in determining whether a pharmacy has crossed the line into manufacturing, and concluded that the First Amendment precludes FDA from using advertising as a factor. Specifically, the Supreme Court wrote "[t]he government thus believes that conditioning an exemption from the FDA approval process on refraining from advertising is an ideal way to permit compounding and yet also guarantee that compounding is not conducted on such a scale as to undermine the FDA

⁶ Woodcock Memorandum at 10, 36.

approval process.” Thompson v. Western States Medical Center, 535 U.S. 357, 371 (2002). The Supreme Court rejected this argument stating “[i]f the First Amendment means anything, it means that regulating speech must be a last -- not first -- resort.” Id. at 373.

Therefore, the fact that compounding pharmacies that compound customized BHRT preparations upon receipt of a valid prescription or physician order also advertise their ability to compound BHRT preparations and distribute educational materials about BHRT products to patients and physicians is irrelevant to the determination of whether the pharmacy is engaged in manufacturing. FDA has recognized this, and removed advertising as a factor to be considered from its Compliance Program Guide Manual, Section 460.200.⁷

III. Compounded Medications are not Unapproved New Drugs and do not Require New Drug Approval

Paradoxically, Wyeth argues both that compounded BHRT preparations are copies of Wyeth’s mare-urine based drugs,⁸ while at the same time (and on the same page)⁹ arguing that the compounded BHRT preparations are unapproved new drugs that are compounded using bulk active ingredients that are not components of FDA-approved drugs.

This is nothing more than a wholesale attack on pharmacy compounding in an effort to maintain Wyeth’s near monopoly on HRT. In effect, Wyeth is attacking the compounding of BHRT by saying that each formulation has not been proven safe and

⁷ IACP does not agree that the Compliance Program Guide (CPG) has any force but it is noteworthy that FDA recognizes, as it must, that advertising may not be considered in determining whether a pharmacy is manufacturing.

⁸ We demonstrate *supra*, p.4, that there can be no copies of Wyeth’s drugs.

⁹ Citizen Petition at 11.

effective. Indeed, FDA itself has expressly recognized that compounding pharmacies need not demonstrate safety and efficacy.

[T]he government also acknowledges that “because obtaining FDA approval for a new drug is a costly process, requiring FDA approval of all drug products compounded by pharmacies for the particular needs of an individual patient would, as a practical matter, eliminate the practice of compounding, and thereby eliminate availability of compounded drugs for those patients who have no alternate treatment.” [Citation omitted.] The government argues that eliminating the practice of compounding drugs for individual patients would be undesirable...

Western States at 369.

Thus, both FDA and the Supreme Court have already acknowledged the importance of pharmacy compounding, and rejected Wyeth’s assertion that compounding pharmacies need to obtain FDA approval prior to compounding individualized prescriptions for BHRT products. Wyeth’s argument that all compounded BHRT must be shown safe and effective should be seen for what it is: an attack on the practice of compounding in an effort to protect Wyeth’s market position.

IV. Wyeth Misleadingly Asserts that Compounded BHRT Preparations have the Same Risk Profile as Wyeth’s Products

Wyeth suggests that the Women’s Health Initiative (WHI) studied bioidentical hormone therapies. It did not. Rather, WHI studied Wyeth’s products exclusively and the study was cut short in 2002 after the data demonstrated that Premarin® (conjugated estrogen) increased the risk of stroke and the components of Prempro®, Premarin plus the progestin medroxyprogesterone acetate (synthetic progesterone), increased the risk of

strokes, breast cancer, heart attacks and blood clots. The physical components of BHRT are different from the components of Wyeth's synthetic hormones that were studied by WHI. WHI did not determine BHRT carries the same risks as Wyeth's products because it did not study BHRT.

V. Wyeth Mistakenly Asserts that BHRT Pharmacies Must Comply with Current Good Manufacturing Practices and References a Discredited "Survey" Conducted by FDA

Wyeth asserts that BHRT pharmacies are required to comply with current good manufacturing practices (cGMPs).¹⁰ This is clearly false. Manufacturers are required to comply with cGMPs. Pharmacies that compound and dispense prescriptions as part of the physician/patient/pharmacist triad do not need to comply with cGMPs. Indeed, given the nature of extemporaneous compounding to meet the unique needs of a patient, an extemporaneously compounding pharmacy could not meet all the elements of pharmaceutical cGMPs. This is another attack by Wyeth on compounding. FDA has not applied cGMPs to pharmacies that extemporaneously compound.

Moreover, Wyeth references a "survey" conducted by FDA to express its concern over quality of compounded drugs.¹¹ Wyeth fails to note that FDA was severely criticized for the use of this analytically flawed and faulty "study" and is itself not relying upon this survey. In a colloquy between Dr. Steven Galson, the Director of the Center for Drug Evaluation and Research at FDA and Senator John Ensign (R-NV), Dr. Galson stated "I want to emphasize that this was not a comprehensive scientific survey. It was a small sample size." Senator Ensign responded: "I normally don't take witnesses to task,

¹⁰ Citizen Petition, 34-35.

¹¹ Id. at 35.

Dr. Galson, but I do want to take you to task on something. You're a scientist, and to present nonscientific data studies . . . is problematic . . . you presented that in a fashion that is misleading." Dr. Galson replied "I wasn't trying to present these as scientific data."¹² Wyeth's citation of this "survey" is itself problematic and misleading.

VI. Wyeth Incorrectly States that IACP Disapproves of BHRT Advertising Claims

Wyeth points to IACP's general guidance statements on advertising by compounding pharmacies and its Code of Ethics, and concludes that "even the compounding pharmacy industry representatives consider the advertising claims being made by many BHRT compounding pharmacies to be misleading and inconsistent with the industry's ethics . . ."¹³ IACP categorically disagrees with this statement.

First, compounding pharmacists are health care professionals, not members of an "industry." Second, IACP takes no position with regard to any advertising or promotional materials disseminated by its individual members. IACP offers its guidance on advertising and has a Code of Ethics that its members can follow. Each pharmacist, in his or her own professional judgment and consistent with state pharmacy laws and ethics, decides what to say in advertising or promotional materials.

In fact, existing FTC regulations already address the issues Wyeth raises. This is an enforcement issue and requires no changes to existing regulations.

¹² U.S. Senate Health, Education, Labor and Pensions Committee Hearing on Pharmacy Compounding, October 23, 2003

¹³ Citizen Petition at 30.

VII. Compounding Pharmacies Need not Include a Brief Summary with their Advertisements nor Include Adequate Directions for Use

Wyeth asserts that compounding pharmacies are in violation of the Federal Food, Drug, and Cosmetic Act (FDCA) because they do not include the brief summary required by FDCA § 502(n) or adequate directions for use required by FDCA § 502(f). Both assertions are incorrect. First, the brief summary requirement applies to the “manufacturer, packer, or distributor” of the drug.¹⁴ Pharmacies that extemporaneously compound drugs upon receipt of prescriptions are not manufacturers, packers, nor distributors of drugs, and FDA has never asserted that they are subject to this requirement. Wyeth, somewhat nonsensically, points to the definition of “distributor” found in regulations implementing the Prescription Drug Marketing Act of 1987. See 21 C.F.R. § 203.3(h). This definition is applicable only to the issue of wholesaler and distributor licensing to distribute prescription drugs and is irrelevant to the discussion of inclusion of brief summaries in advertisements. Moreover, Wyeth is confused when it cites the list of activities included in 21 C.F.R. § 201.1(b) to conclude that pharmacies are manufacturers. Again, FDA has never taken the position that pharmacies that engage in extemporaneous compounding upon receipt of a prescription are manufacturers, simply because they may, in the course of compounding, engage in one or more of the activities listed in § 201.1(b).

Further, compounded drugs dispensed to patients are exempt from the requirement that they contain “adequate directions for use.” Wyeth is well aware of this exemption, since they cite the very provision that exempts drugs dispensed by pharmacists from the “adequate directions for use” requirement, FDCA § 503(b)(2), on the very next page after

¹⁴ FDCA § 502(n).

their assertion that compounded drugs need to comply with the "adequate directions for use" requirement.¹⁵

VIII. Other Organizations that Have Filed in Support of Wyeth's Petition are not Independent, but Have Financial Links to Wyeth

As of December 12, 2005, several organizations have filed comments with FDA in support of Wyeth's petition. These groups include: Society for Women's Health Research; Jacob's Institute for Women's Health; American Medical Women's Association; National Association of Nurse Practitioners in Women's Health; National Black Women's Health Project, the American Society of Reproductive Medicine, and the North American Menopause Society.

Each of these organizations is, to varying degrees, financially linked to Wyeth and, as a result, their comments should not be viewed as independent. The following illustrations are just that and are not intended to represent the full extent of these organizations' links to Wyeth:

- On its web site, American Medical Women's Association lists Wyeth as one of nine members of its Corporate Partners Program, which it "thank[s] for their generous support."¹⁶
- Wyeth serves on Society for Women's Health Research's Corporate Advisory Team.¹⁷

¹⁵ Citizen Petition at 24, n.17.

¹⁶ <http://www.amwa-doc.org>

¹⁷ <http://www.womenshealthresearch.org/about/cac.htm>

- Wyeth also serves on the Jacobs Institute's Corporate Advisory Council. In addition, the Jacobs Institute held a seminar on Capitol Hill on December 7, 2005, during which doctors and journalists discussed the media's and the public's reaction to the Women's Health Initiative (WHI) study, which found that Premarin® (conjugated estrogen) increased the risk of stroke and the components of Prempro®, Premarin plus the progestin medroxyprogesterone acetate (synthetic progesterone), increased the risk of strokes, breast cancer, heart attacks and blood clots. At this event, several speakers with financial ties to Wyeth suggested that Wyeth's hormone treatments were less dangerous than the media and, subsequently, patients and doctors perceived. According to the Jacobs Institute website, the briefing was sponsored "by an unrestricted educational grant from Wyeth."¹⁸
- Susan Wysocki, president and CEO of National Association of Nurse Practitioners in Women's Health, serves on both the advisory board and the speakers bureau for Wyeth.¹⁹
- The American Society of Reproductive Medicine received at least \$75,000 from Wyeth this year, which was in the top echelon of sponsors of its annual meeting.²⁰
- The National Black Women's Health Project has received money from Wyeth for events.²¹
- The North American Menopause Society features at least three Wyeth-sponsored awards to physicians and nurses.²²

¹⁸ <http://www.jiwh.org>

¹⁹ <http://www.npwh.org/CE-Transdermal/article1.htm>

²⁰ <http://www.asrm.org/Professionals/Meetings/annualmeeting.html>

²¹ <http://www.blackwomenshealth.org/site/News2?page=NewsArticle&id=6388&JServSessionIdr011=t2lyv0bu91.app2a>

In addition, while the American College of Obstetricians and Gynecologists has not filed a comment with the FDA, it did issue a statement echoing many of the points in Wyeth's filing. This organization, like the others, also has ties to Wyeth. For example, Wyeth is an official "Friend of ACOG," a distinction that corporations may earn by paying annual dues of at least \$3,000. The College also issues an annual Wyeth Pharmaceuticals Section Award, which is worth \$5,000.²³

* * *

We appreciate the opportunity to submit these comments and request FDA deny Wyeth's meritless petition.

Sincerely,



L.D. King
Executive Director
International Academy of Compounding Pharmacists

²² <http://www.menopause.org/awards.htm>

²³ [http://www.acog.org/departments/dept_notice.cfm?recno=41&bulletin=3083;
http://216.239.51.104/search?q=cache:c6K23xULvJIJ:www.acog.org/from_home/
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